



Application No.: 09/853,427

Attorney Docket No.: MUL01-NP001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of) Examiner: Ungar, Susan
James Mullin et al.)
Serial No.: 09/853,427) Group Art Unit: 1642
Filed: May 10, 2001)
For: "EARLY DIAGNOSIS OF) Response to paper No.: 14
CANCEROUS AND)
PRECANCEROUS CONDITIONS)
BY LEAKAGE OF SIGNATURE)
PEPTIDES AND)
CARBOHYDRATES INTO THE)
BLOODSTREAM")

RECEIVED

OCT 29 2003

TECH CENTER 1600/2900

DECLARATION OF JAMES M. MULLIN UNDER 37 C.F.R. §1.132

I, James M. Mullin, hereby declare that:

1. I am a citizen of the United States and reside at 17 Orchard Road, Havertown, PA 19083.

2. I received a B.S. degree in Biology from St. Joseph's College and Ph.D. degree in Physiology from the University of Pennsylvania. Additional details of my educational background are set forth in my *Curriculum vitae*, attached hereto.

3. I have over 30 years of experience in the field of physiology, cancer research, and gastroenterology.

4. I am the author or co-author of over 50 scientific articles on the subjects of gastroenterology and cancer research. A list of these articles is set forth in my

curriculum vitae, attached hereto. My current areas of research include the regulation of the barrier function of epithelia, and its failure in certain pathophysiological conditions.

5. I am a co-inventor of the subject matter disclosed and claimed in U.S. Patent Application Serial No. 09/853,427, entitled "Early Diagnosis of Cancerous and Precancerous Conditions by Leakage of Signature Peptides and Carbohydrates into the Bloodstream" (hereinafter "the '427 application"). I understand that, claims 3-12 are rejected.

6. I have read and am familiar with the Official Action dated June 17, 2003 in the '427 application. I understand the nature of the rejections made by the Examiner concerning an alleged lack of utility and enablement. In particular, I understand that it is the Examiner's position that claims 3-12 lack utility as the specification has allegedly failed to provide clear evidence of the correlation between sucrose levels in urine and precancerous conditions of esophageal mucosa in a patient. I also note the Examiner's position that claims 3-12 are allegedly not enabled as the specification does not provide clear evidence of the correlation between these levels nor examples for practicing the claimed invention. As a co-inventor of the subject matter of the present application, I strenuously disagree with the Examiner, for the reasons set forth in the following paragraphs.

7. As exemplified in the specification, my co-inventors and I have devised a method for diagnosing precancerous conditions in esophageal mucosa, e.g., Barrett's esophageal condition based on the levels of at least one carbohydrate, such as sucrose or mannitol, in a patient's urine sample. The

method may further comprise a biopsy examining tight junction (TJ) leakiness of an esophageal mucosal sample from the patient.

8. Contrary to the Examiner's assertion, evidence showing the correlation between urine sucrose levels and precancerous conditions in esophageal mucosa, such as Barrett's esophagus, are provided in the specification as originally filed. As set forth at page 14, lines 17-33, sucrose is an excellent marker for TJ leakiness in the upper GI tract and defects in the gastric barrier result in the diffusion of undegraded sucrose into the bloodstream allowing for its subsequent quantitative appearance in blood and subsequently urine. It is also disclosed at page 8 that aberrant TJ or TJ leakiness is associated with tumors and transformation. Further experimental basis **supporting and validating** the correlation between elevated urine sucrose levels and Barrett's esophagus is provided hereinbelow:

Sucrose Leak Data for Barrett's Esophagus Study:

In order to study whether sucrose levels are elevated in urine in the presence of precancerous conditions of esophageal mucosa, such as Barrett's esophagus, patient volunteers were asked to drink a solution of 100 gms of sucrose in 200 cc of water at bedtime and any urine voided for the next 6-8 hours were collected for analysis of sucrose levels therein. Four patient groups, with two separate groups of "control" were employed in the study. Group A (first control group) includes 15 patients who are not endoscoped. These patients are asymptomatic for reflux and are not taking proton pump inhibitors (PPIs). Group B (second control group) includes 5 patients who are endoscoped and visually free of Barrett's or other esophageal mucosal disorders or gastric mucosal disorders.

These patients are also asymptomatic for reflux but are appearing for endoscopy for other medical reasons, such as cancer screening (unusual for the upper GI tract) or dysphagia (hiatal hernia or Schatzke's ring). Group C includes 10 patients who are endoscoped and found to be free of Barrett's or esophagitis (or gastric mucosal disorders) but are symptomatic for reflux. These patients are typically on PPIs for their reflux. Group D includes 10 patients who are symptomatic for reflux and found to also contain Barrett's metaplasia in their distal esophagus after endoscopy and histology. None of these patients, however, has esophageal cancer nor is dysplasia found within the Barrett's metaplasia.

As shown in Table 1 and Figure 1, the two control groups overlap and show no statistical difference ($P = 0.45$, Student's t test, unequal equal variances). These groups also show a fairly tight range of urine sucrose levels (17 to 86 mg). The reflux (only) group (range of 21 to 118 mg) shows a slightly higher but statistically non-significant difference in urine sucrose levels than the two control groups. The Barrett's group (range of 39 to 369 mg), however, shows a small degree of overlap with the control groups (A and B) and the reflux only group (C) but the levels of sucrose present in urine are statistically different from both control and reflux only groups.

Table 1. Data Summary (Urine Sucrose Levels)

	Group A	Group B	Group C	Group D
N	15	5	10	10
Mean	66 mg \pm 13 mg + 7 mg	60 mg \pm 25 mg + 11 mg	82 mg \pm 42 mg + 13 mg	153 mg \pm 93 mg + 30 mg
Min	41 mg	17 mg	21 mg	39 mg
Max	86 mg	80 mg	118 mg	369 mg

Group A: Non Endoscoped Controls

Group B: Endoscoped Controls

Group C: Reflux Only

Group D: Barrett's

N: Number of Subjects

Student *t* test data comparisons:

A vs D: P = 0.0016

B vs D: P = 0.050

C vs D: P = 0.042

A vs B: P = 0.452 (NS)

A vs C: P = 0.187 (NS)

B vs C: P = 0.292 (NS)

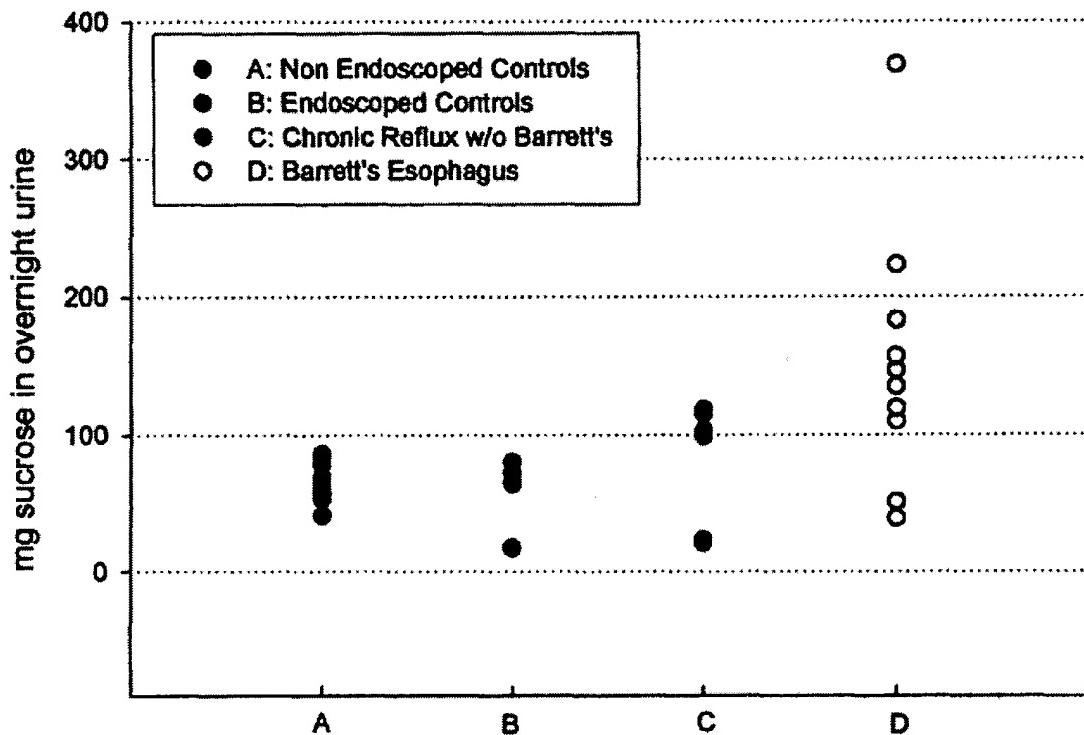


Figure 1

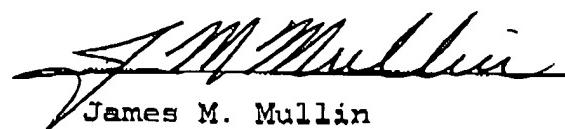
Application No.: 09/853,427

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These data clearly demonstrate that elevated urine sucrose levels are correlated with Barrett's esophagus, a precancerous condition in the esophageal mucosa.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the above-referenced application or any patent issued thereon.

10/17/03
DATE


James M. Mullin

CURRICULUM VITAE

James M. Mullin, Ph.D.

Home Address: 27 Orchard Road
Havertown, PA 19083

Office Address: The Lankenau Institute for Medical Research
100 Lancaster Avenue
Wynnewood, PA 19096
Phone: (610) 645-2703
Fax: (610) 645-2205

Social Security #: 197-46-1440

Citizenship: United States

EDUCATION

1972-76 B.S. St. Joseph's College (Biology, Summa cum laude)
1976-80 Ph.D. University of Pennsylvania (Physiology)

POSTGRADUATE TRAINING AND FELLOWSHIP APPOINTMENTS

1980-82 University of Pennsylvania, Department of Physiology & Wistar Institute
Advisors: Drs. Arnost Kleinzeller and Leila Diamond
1982-84 Yale University, Department of Human Genetics
Advisors: Drs. Carolyn Slayman and Edward Adelberg

RESEARCH AND CLINICAL STAFF APPOINTMENTS

1984-86 Research Associate
Wistar Institute of Anatomy and Biology, Philadelphia, PA
1986-1995 Investigator, The Lankenau Medical Research Center, Wynnewood, PA
1990-1995 Adjunct Assistant Professor, Dept. of Biochemistry, University of
Pennsylvania School of Medicine, Philadelphia, PA
1995-present Senior Investigator, The Lankenau Medical Research Center, Wynnewood, PA
2002-present Associate Member, Department of Medicine, Division of Gastroenterology,
Lankenau Hospital, Wynnewood, PA
2002-present Adjunct Professor, Department of Biology, St. Joseph's University,
Philadelphia, PA

AWARDS

1982 National Science Foundation Postdoctoral Fellowship
1983 National Institutes of Health Postdoctoral Fellowship

SERVICE

- 1989-1991 Building/Planning Committee for new laboratory complex, Lankenau Institute for Medical Research, Wynnewood, PA
- 1988-1999 Seminar Committee Chair, Lankenau Institute for Medical Research, Wynnewood, PA
- 2001-present Animal Care and Use Committee, Lankenau Institute for Medical Research, Wynnewood, PA
- 2001-present Appointments and Promotions Committee, Lankenau Institute for Medical Research, Wynnewood, PA
- 2002-present Joint Graduate Education Committee, Lankenau Institute for Medical Research, Wynnewood, PA

EDUCATION ACTIVITIES

- 1978-1980 Laboratory instructor (feline hemodynamics and cardiac contractility) for General Physiology course for Medical School students, Dept. of Physiology, Univ. of Pennsylvania
- 1979-1982 Laboratory instructor (^{22}Na efflux from skeletal muscle) for Cell Physiology course for graduate students, Dept. of Physiology, Univ. of Pennsylvania
- 1988- present Laboratory semester rotations for college students, Dept. of Biology, Rosemont College, Rosemont, PA (Ms. Linda Kofeldt; Ms. Mary Hagee, Ms. Anne Guy, Ms. Michelle Nuciglio)
- 1995 Laboratory rotation, Ms. Cheryl Clarkin, Dept. of Biochemistry, Univ. Pennsylvania Sch. Medicine
- 1998- present Laboratory semester rotations for college students, Dept. of Biology, Neumann College, Aston, PA (Ms. Maria Ropas, Ms. Laura Henderson)
- 1999 Dissertation committee, Ms. Yvonne Naughton, Dept. of Pharmacology, Univ. College Dublin, Dublin, Ireland
- 2001 Dissertation committee, Ms. Bridget Kiely, Dept. of Pharmacology, Univ. College Dublin, Dublin, Ireland

MEMBERSHIPS IN PROFESSIONAL SOCIETIES

- 1976 - present American Physiological Society
- 1988 - present American Assn. Cancer Research
- 1998 - present American Gastroenterological Assn.

EDITORIAL POSITIONS

Editorial Board

- 1991 - 1993 The American Journal of Physiology (Renal)

JOURNAL REVIEW

- 1986 - present The American Journal of Physiology (Cell)

- 1995 - present The American Journal of Physiology (Renal)
 The Journal of Membrane Biology
 The Journal of Cell Science
 Kidney International
 J. of Cellular Physiology
 Proc. Natl. Acad. Sci (USA)

GRANT REVIEW BOARDS

- | | |
|-----------|---|
| 1990-1991 | National Kidney Fndn. (Philadelphia Chapter), Grant Review Committee |
| 1993 | Ad Hoc Reviewer, Natl. Inst. Health |
| 1994 | Ad Hoc Reviewer, Kidney Fndn. of Canada |
| 1997 | Ad Hoc Reviewer, Alberta Heritage Fndn., Canada |
| 2000 | National Institutes of Health (NIDDK) Program Project Site Visiting Team,
Boston, MA |
| 2000-2001 | Lowe's Foundation |

PRINCIPAL INVESTIGATOR OF GRANTS

1. Renal Glucose Transport and Synthesis, National Institutes of Health, AM 36721, 1985-1988
 2. Epithelial Cell Division-Polarity and Phorbol Esters, National Institutes of Health, CA 48121, 1988-1993
 3. Cocarcinogens & Epithelial Barriers: Model for Neoplasia, National Institutes of Health, CA 48121, 1993-1998
 4. Cytokines, Transepithelial Permeability and Colitis, N.I.H. Award to hold a research conference in Philadelphia, September 1998
 5. Aging and Tight Junction Permeability, National Institutes of Aging, RO3-AG18643, 2000- 2001
 6. Leakiness of Gastrointestinal Tight Junctions in Premalignant Conditions, John S. Sharpe Foundation, 2001 – 2002.

LECTURE BY INVITATION

- 1988 "EGF Induced Cell Division in Polar Epithelia: Basolateral Site of Action" - Dept. of Biochemistry, Temple University School of Medicine, Phila., PA

1988 Symposium: "Cell Culture as a Tool to study Transport Processes" - American Association Pharmaceutical Scientists, Orlando, FL "Protein Kinase C Control of Epithelial Barriers"

1989 "Regulation of Epithelial Tight Junction Permeability" Interex Corp. and the Dept. of Pharmacology, Univ. of Kansas, Lawrence, Kansas.

1991 "Regulation of Epithelial Tight Junctions" Dept. of Physiology and Biophysics, Univ. of Texas School of Medicine, Galveston, TX

1991 "Regulation of Transepithelial Permeability by Tumor Necrosis Factor" Eli Lilly and Company, Indianapolis, IN.

1993 "The Regulation of Tight Junction Permeability in Epithelial Cancers" Fox Chase Cancer Center, Phila., PA

1994 "Regulation of Tight Junctions by Tumor Necrosis Factor" FASEB Symposium (Am.

- Physiol. Soc.), Anaheim, CA.
- 1994 "Regulation of Tight Junctions by Protein Kinase C Isoforms" Dept. of Physiology, Univ. of Alberta School of Medicine, Edmonton, Canada
- 1996 "Role of Tight Junctional Leakiness in Epithelial Cancer", Mount Desert Island Biol. Lab., Salisbury Cove, Maine
- 1999 "Tight Junction Regulation by Protein Kinase C and Phorbol Esters," International Symposium on Epithelial Transport and Barrier Function in Gastrointestinal Disorders, Berlin, Germany.
- 1999 "Effect of TNF-Induced Apoptosis on Epithelial Barrier Function," University of Hannover School of Medicine, Germany.
- 1999 "Effect of Phorbol Esters and Bryostatins on Epithelial Barrier Function," Univ. of Frankfurt School of Medicine, Germany.
- 1999 "Protein kinase C regulation of epithelial tight junctions," Department of Pharmacology, University College Dublin, Ireland
- 2001 "Epithelial tight junctional leakiness in cancer," Department of Pharmacology, University College Dublin, Ireland
- 2002 "Failure of gastrointestinal epithelial barrier function in disease," - Canadian Gastroenterological Assn., Montreal, Canada

BIBLIOGRAPHY

Original Papers

1. Kleinzeller, A., Dubyak, G.R., and Mullin, J.M. 1976. Renal sugar transport in the winter flounder. II. Galactose transport system. Am. J. Physiol. 231: 608-613.
2. Kleinzeller, A., Dubyak, G.R., Griffin, P.M., McAvoy, E.M., Mullin, J.M., and Rittmaster, R. 1977. Renal sugar transport in the winter flounder. III. Two glucose transport systems. Am. J. Physiol. 232: F227-F234.
3. Kleinzeller, A., Dubyak, G.R., Mullin, J.M., and McAvoy, E.M. 1977. The phlorizin effect on the transport of sugars at the antiluminal face of teased flounder tubules. J. Exp. Zool. 199: 391-394.
4. Mullin, J.M., Weibel, J., Diamond, L., and Kleinzeller, A. 1980. Sugar transport in the LLC-PK₁ cell line: Similarity to mammalian kidney and the effect of cell density. J. Cell. Physiol. 104 (3): 375-389.
5. Mullin, J.M., Diamond, L., and Kleinzeller, A. 1980. Effects of ouabain and ortho-vandate on transport-related properties of the LLC-PK₁ renal epithelial cell line. J. Cell. Physiol. 105(1): 1-6.
6. Mullin, J.M., Weibel, J., Diamond, L., and Kleinzeller, A. 1980. Transport-related properties and the development of polarity of an established epithelial cell line of renal origin. Symposia of the XXVIII International Physiological Congress (L. Takacs, ed.), Pergamon Press.
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8. Adler, E., Fluk, L., Mullin, J.M., and Kleinzeller, A. 1982. Anomalous patterns in cultured cell monolayers. Science 217 (4562): 851-853.

9. Mullin, J.M., Fluk, L., and Tchao, R. 1985. Mitosis in domes of renal epithelial cell cultures. *Mol. Physiol.*, 8: 317-328.
10. O'Brien, T.G., Saladik, D., Sina, J.R., and Mullin, J.M. 1982. Formation of a glucuronide conjugate of TPA by LLC-PK₁ renal epithelial cells in culture. *Carcinogenesis* 3(10): 1165-1171.
11. Mullin, J.M., Fluk, L., and Kleinzeller, A. 1986. Basal-lateral transport and transepithelial flux of alpha-methyl-D-glucoside across LLC-PK₁ renal epithelia. *Biochim. Biophys. Acta*, 885: 233-239.
12. Mullin, J.M. and Kleinzeller, A. 1985. Sugar transport in the renal epithelial cell culture. In: *Tissue Culture in the Study of Epithelial Transport* (M. Taub, ed.). New York: Plenum Press, 71-85.
13. Mullin, J.M. and O'Brien, T.G. 1986. Effects of tumor promoters on LLC-PK₁ renal epithelial tight junctions and transepithelial fluxes. *Am. J. Physiol.* 251: C597-C602.
14. Fairgrieve, M., Mullin, J.M., Dantzig, A.H., Slayman, C.W., Adelberg, E.A. 1987. Isolation and characterization of a glycine transport mutant in an established mammalian cell line, CHO (PEOT/1). *Somatic Cell Genetics* 13:505-512.
15. Mullin, J.M. and McGinn, M.T. 1987. The phorbol ester, TPA, increases transepithelial EGF flux. *FEBS Letters* 221:359-364.
16. Mullin, J.M. and O'Brien, T.G. 1987. Spontaneous reversal of polarity of the voltage across LLC-PK₁ renal epithelial cell sheets. *J. Cell. Physiol.* 133:515-522.
17. Mullin, J.M. and McGinn, M.T. 1988. Effects of diacylglycerols on LLC-PK₁ renal epithelia: Similarity to phorbol ester tumor promoters. *J. Cell. Physiol.* 134:357-366.
18. Mullin, J.M. and McGinn, M.T. 1988. Epidermal growth factor-induced mitogenesis in kidney epithelial cells (LLC-PK₁). *Cancer Research* 48:4886-4891.
19. Mullin, J.M., McGinn, M.T., Snock, K.V., and Kofeldt, L.M. 1989. Na⁺-independent sugar transport by cultured renal (LLC-PK₁) epithelial cells. *Amer. J. Physiol.* 257:F11-F17.
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22. Mullin, J.M. and Snock, K.V. 1990. The Effect of tumor necrosis factor on epithelial tight junctions and transepithelial permeability. *Cancer Research*, 50:2172-2176
23. Mullin, J.M., McGinn, M.T., and Snock, K.V. 1991. Effects of apical vs basolateral palytoxin on LLC-PK₁ renal epithelia. *Am. J. Physiol.* 260:C1201-C1211.
24. Mullin, J.M., Kofeldt, L.M., Russo, L.M., Hagee, M.M., and Dantzig, A.H. 1992. Basal-lateral 3-O-Methylglucose transport by cultured kidney (LLC-PK₁) cells. *Am. J. Physiol.* 262:F480-F487.
25. Mullin, J.M., Snock, K.V., Noe, J., Shurina, R.D., George, K., Misner, L., Imaizumi, S., and O'Brien, T.G. 1992. Effects of acute vs chronic phorbol ester exposure on transepithelial and epithelial morphology. *J. Cell. Physiol.* 152:35-47.
26. Mullin, J.M., Russo, L.M., Laughlin, K.V., Marano, C.W. and Peralta Soler, A. 1992. Modulation of tumor necrosis factor-mediated changes in renal (LLC-PK₁) transepithelial

- permeability. *Am. J. Physiol.*, 263:F915-924.
27. Miller, J.H., Mullin, J.M., McAvoy, E., and Kleinzeller, A. 1992. Polarity of transport of 2-deoxy-D-glucose and D-glucose by cultured renal epithelia (LLC-PK₁). *Biochim. Biophys. Acta*, 1110(2):209-217.
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32. Marano, C.W., Laughlin, K.V., Russo, L.M., and Mullin, J.M. 1995. The protein kinase C inhibitor, bisindolylmaleimide Inhibits the TPA-induced but not the TNF-induced increase in LLC-PK₁ transepithelial permeability. *Biochem. Biophys. Res. Commun.* 209:669-676.
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- CACO-2 BBE, a human intestinal epithelial cell line. *J. Membr. Biol.* 161:263-274, 1998.
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47. Clarke, H.M., Peralta Soler, A. and Mullin, J.M. Protein kinase C activation leads to dephosphorylation of occludin and tight junction permeability increase in LLC-PK1 epithelial cell sheets. *J Cell Sci* 113:3187-3196, 2000.
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50. Clarke, H.M., Ginanni, N. Laughlin, K.V. and Mullin, J.M. Regulation of protein kinase C- δ and -epsilon isoforms by phorbol ester treatment in LLC-PK1 renal epithelia. *Kidney Intl.*, 58:1004-1015, 2000.
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54. Mullin, J.M., Valenzano, M.C., Verrechio, J.J., and Kothari, R. Age and diet related increase in transepithelial colon permeability of Fisher 344 Rats. *Dig Dis Sci* 47:2262-2270, 2002.
55. Rendon-Huerta, E., Valenzano, M.C., Hameed, B., Smolen, J.M., Gilliard, G., Mullin, J.

Induction of Gastric Epithelial Dysplasia is Associated with Increased Tight Junction Permeability. *Cancer Res* (submitted)

Book Chapter:

1. Mullin, J.M. and Kleinzeller, A. 1985. Sugar transport in the renal epithelial cell culture. In: *Tissue Culture in the Study of Epithelial Transport* (M. Taub, ed.). New York: Plenum Press, 71-85.

Invited Review:

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Statement of Research Interests

James M. Mullin, Ph.D.

My area of interest is in the regulation of the barrier function of epithelia, and its failure in certain pathophysiological conditions. This normally imparts a focus on the regulation of the paracellular pathway, and most notably its rate limiting step, the tight junction. This general interest comprises two distinct but interrelated diseases: chronic inflammatory states and cancer. For both programs this research encompasses studies at the molecular level using epithelial cell cultures, and studies at the tissue level utilizing colonic tissue from both animal models and human clinical specimens.

In the project dealing with epithelial cancer, my interest has been in the mechanisms by which tumor promoting agents such as phorbol esters stimulate the development of tumors. Our cardinal finding here is that phorbol esters will increase tight junctional permeability through the activation of protein kinase C. This permeability increase extends not simply to salts and water, but macromolecules as well. We have recently demonstrated that protein kinase C activation can lead to 40-fold increases in the transepithelial passage of insulin and epidermal growth factor. The biological significance to this phenomenon resides in the innate polarity of epithelia, and the tendency of epithelial tissues to synthesize and secrete growth regulatory proteins into their luminal fluid compartments. Since growth factor receptors are normally localized to the basal-lateral or abluminal cell surface, the very high concentration of e.g. epidermal growth factor in urine will not affect the cell kinetics of the lower urinary tract. If however a preneoplastic focus of cells develop chronically leaky tight junctions, these cells will be under constant stimulation by growth factors entering their lateral intercellular spaces from the luminal compartment. We believe that this phenomenon is responsible for the promotional phase of many epithelial cancers. Our research is now focused on the exact protein kinase C isoforms which are involved in this leakiness, how far upstream protein kinase C is located in this overall signal transduction pathway, and the structural target proteins whose phosphorylation state is being altered thereby changing tight junctional permeability. We are also currently engaged in identifying the signaling pathway which acts in opposition to protein kinase C, and maintains junctions in a relatively non-leaky state.

The project involved in epithelial inflammation focuses on the transepithelial (paracellular) leakiness which the cytokine, tumor necrosis factor (TNF), causes in epithelial barriers. We have observed that TNF induces paracellular leakiness by engendering increased rates of apoptosis in the epithelium. However this leakiness extends only to relatively small molecules. Quite surprisingly, the apoptotic cells are never simply shed from the epithelium, creating holes in the barrier as they leave. Instead the apoptotic cells are normally phagocytized by their neighboring epithelia, assuring among other things, that actual holes never develop. Our research is now focused on the TNFR1 receptor initiated signaling events that trigger increased motility in the cells surrounding the apoptotic sites, and the pathophysiological conditions such as ischemia which can forestall this process, thereby creating major leakiness which is both sustained and extending to large molecules. In addition to using cell lines such as LLC-PK1 and CACO-2, we are also using animal models such as the HLA-B27 rat and the IL-10 knockout mouse, as well as colonoscopy and surgical tissue samples from patients with inflammatory bowel disease. Our goal is to understand whether TNF-

induced signaling per se or the presence of a neighboring apoptotic cell is the triggering mechanism for the increased motility of the non-apoptotic epithelia, and whether the paracellular leakiness is occurring only at apoptotic sites or is more general across the entire epithelium. Beyond that we wish to determine which signaling elements downstream from the TNFR1 receptor (e.g. the TRAF2 vs the FADD pathway) are involved in these changes in barrier function.

In summary, both projects are well suited to my overall desire to conduct molecular research with direct clinical application, and be able to personally "move" that research from the cell culture level on through to patient-based research. Understanding the paracellular permeability changes accompanying carcinogenesis and chronic inflammation in epithelial tissues, should deliver up new diagnostic as well as therapeutic approaches to these diseases.

References:

Bonnie L. Blazer-Yost, Ph.D.
Dept. of Biology
Indiana U. - Purdue U. at Indianapolis
723 W. Michigan St.
Indianapolis, IN 46202-5132
317-278-1145
317-274-2846 (fax)

Anne H. Dantzig, Ph.D.
Research Scientist
Dept. of Cancer Research
Lilly Research Labs.
Lilly Corporate Center
Indianapolis, IN 46285-0424
317-276-5083
317-276-9086 (fax)

Simon A. Lewis, Ph.D.
Dept. of Physiology and Biophysics
Univ. of Texas Medical Branch
Galveston, Texas 77555-0641
409-772-3397
409-772-3381 (fax)

Bruce R. Stevenson, Ph.D.
Dept. of Anatomy and Cell Biology
Faculty of Medicine
University of Alberta
Edmonton, Alberta
Canada T6G 2H7
403-492-1841
403-492-0450 (fax)

A.J.P. Klein-Szanto, M.D.
Dept. of Pathology
Fox Chase Cancer Ctr.
7701 Burholme Avenue
Philadelphia, PA 19111
215-728-3154
215-728-2899 (fax)